REMARKS

Claims 43-45, 61, 63-64 are pending in this application. Claims 43-45, 61, and 63-64 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement and written description. Claims 43, 45, and 64 were rejected under 35 U.S.C. § 112, second paragraph. Claims 43-45, 61, and 63-64 were rejected under 35 U.S.C. § 102(b). Each of these rejections is addressed as follows.

Amendments

Claims 43-44 have been amended to remove "a marker co-expressed and/or co-detectable with CDMP-1."

Claims 43-44 have been amended to require a "homogenous culture of viable, differentiated precursor cells..." Support for this amendment is found, for example, on page 20, line 27 through page 21, line 3, of the specification (emphasis added):

> Suitable selection methods are well known in the art. Such selection or enrichment protocols will avoid the unpleasant eventuality of other contaminating tissues arising from the pool of skeletal precursor cells. Once enriched, these cells can be directed to any differentiation pathway such as the chondrogenic pathway, by culturing under consistent and appropriate conditions with or without morphogens/growth factors to end up with a ***homogeneous*** cell population, such as chondrocytes with a phenotypic stability. In particular, the present invention shows that periosteum, bone marrow, and synovial membrane contain CDMP-1 expressing skeletal precursor cells that can be committed towards chondrogenesis using appropriate culture conditions. In contrast to previous studies of Nakahara et al. (1991), J. Orthop. Res. 9: 465-76, the present invention shows that regardless of donor age, human skeletal precursor cells are easily accessible and expandable and can be induced consistently to differentiate into chondrocytes.

Claims 61 and 64 have been amended to remove the recitation of "another marker of the mature chondrocyte phenotype" to instead specifically recite the markers of mature chondrocytes, including FGFR3, type II collagen, type X collagen, and BMP-2. Support

for this amendment is found, for example, on page 17, line 34, to page 18, line 3, of the specification:

> For instance, when skeletal precursor cells differentiate into chondrocytes, the expression of cartilage markers such as type II collagen, FGFR3, type IX collagen, or type XI collagen is always preceded by the disappearance of CDMP-1. Markers such as FGFR3, type II collagen, type IX collagen, or type XI collagen or markers or co-detectable with these markers are negative markers.

Support for this amendment is also found, for example, on page 31, lines 8-15, of the specification:

> It can be seen that CDMP1 is strongly downregulated as skeletal precursor cells enter chondrogenesis and mature to chondrocyte phenotype. The mature chondrocyte phenotype is heralded by the appearance of type II collagen, type X collagen, FGFR3 (fibroblast growth factor 3) and BMP2. A positive marker in accordance with the present invention such as the CDMP-1 marker or a marker or factor co-expressed or co-detectable with this marker, and a negative marker such as the chondrocyte markers type II collagen, type X collagen, FGFR3 and BMP2 or a marker co-expressed or co-detectable with any or all of these markers, are mutually exclusive.

Applicants note that the present amendments were made solely to advance prosecution and reserve the right to pursue cancelled subject matter in this or a continuing application.

Rejections under 35 U.S.C. § 112, first paragraph (enablement)

Claims 43-45, 61, and 63-64 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. For the following reasons, this rejection should be withdrawn. The claims, as amended, are directed to a homogeneous culture of viable, differentiated precursor cells retaining the intrinsic potential of

multilineage differentiation. The cells were isolated from periosteum, bone marrow, or synovial membrane, and have entered a post-natal skeletal differentiation pathway leading to the formation of skeletal or connective tissue, wherein the cells express an embryonic marker which is CDMP-1. Dependent claims relate to the absence of negative markers, i.e., the absence of markers characteristic of mature chondrocytes such as FGFR3, type II collagen, type IX collagen, type X collagen, type XI collagen, and BMP-2.

It was asserted in the final Office Action that a skilled person could not use markers that are co-expressed or co-detectable with CDMP-1 to uniquely identify the cell populations as claimed. However, it was noted that the specification is enabling for the CDMP-1 marker. Without acquiescence to this assertion, the currently presented claims solely refer to the CDMP-1 marker and are, to the Examiner's own acknowledgement, enabled by the present specification.

The Examiner has argued that the dependent claims specifying that the cells, therapeutic composition, cell culture, and implants including these cells, are further characterized by the absence of negative markers are also not enabled and not within the scope of the claims. Without acquiescence to this assertion, the currently presented claims are directed to a selection of a discrete population of markers, which must be undetectable within the cells of the invention.

Applicants submit that the Examiner's reasoning with regard to the negative markers characterizing the precursor cells of the present invention is inappropriate. The Examiner indicates that "the specification teaches that the mature chondrocyte phenotype is heralded by the expression of all of the recited markers" and that "there is no guidance provided by the specification to show the mature chondrocyte phenotype can be a combination of any of these markers" (Office Action, page 5). Applicant respectfully submits that, irrespective of whether or not "mature chondrocyte phenotype" is characterized by all of these markers, the present application clearly states that the precursor cells of the present invention can be identified by the expression of "a positive

marker" and/or the absence of expression of "a negative marker." Thus, the invention does not require the identification of all positive and/or all negative markers potentially associated with the mature chondrocyte phenotype.

Furthermore, Applicants respectfully point out that the Examiner has provided an improper interpretation of claim 61 as amended by the Applicants in their response to the Office Action that was mailed on June 27, 2006. According to the Examiner in the final Office Action, "(c)laim 61 requires that the cells are characterized by the absence of a negative marker (FGFR3), or a marker or factor co-expressed or co-detectable with FGFR3" (Office Action, page 6). Claim 61, as amended in the response filed on September 27, 2006, was submitted as follows:

> 61. The therapeutic composition of claim 44, wherein said viable, differentiated precursor cells that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue are further characterized by the absence of negative markers, said negative markers being FGFR3 or another marker of the mature chondrocyte phenotype.

As such, claim 61, as amended, was not properly construed.

The Examiner has further argued "the absence of expression a negative marker [*sic*] is not within the broad scope of the claims, which requires a marker that is either expressed or detectable with CDMP-1 (see claims 43-45). A negative marker is not expressed" (Office Action, pages 5-6; emphasis original). Applicants strongly disagree.

Applicants assert that dependent claims 61 and 63-64 have been improperly read in light of claims 43-44. Indeed, the Examiner considers that, because claims 43-45 are directed to markers expressed in the cells of the invention, any dependent claims thereof should also be limited to markers that are also expressed and not to markers that are absent. Applicants assert that a dependent claim is used to further characterize the invention and that there is no obligation that the further characterizing features be of the same nature as recited in the independent claim from which it depends. For the subject

matter of the claims currently under discussion, it is clear that a cell population can be characterized by the expression of one or more markers and, in addition, can further be characterized by the fact that certain negative markers are not expressed.

Applicants respectfully direct the Examiner's attention to the M.P.E.P., section 608.01(n), where it is stated that "(t)he test for a proper dependent claim is whether the dependent claim includes every limitation of the parent claim. The test is not whether the claims differ in scope" (emphasis original). Therefore, claims 61 and 63-64 are properly dependent claims and their scope is not in opposition to the scope of claims 43-44. In view of the arguments presented above, Applicants submit that the claims as presently amended are fully enabled.

As for the therapeutic benefit of the present invention, the Examiner maintains that the "*in vivo* implantation of the cells by intramuscular injection of the cells into nude mice" is "not analogous to what would be considered a therapeutic treatment" (Office Action, page 8). Applicants respectfully disagree. Applicants submit that, according to the M.P.E.P. 2164.02, "(a)n applicant need not have actually reduced the invention to practice prior to filing. In *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)." Therefore, it is not required that the applicants show, as stated by the Examiner (Office Action, page 9), functional rescue in an animal model of joint defect Additionally, the Examiner has provided no reasoning or evidence as to why cells capable of generating cartilage when injected intramuscularly would fail to do so if implanted in a joint, healthy or not.

Applicants hereby refer to the enclosed declaration by one of the named inventors of this application, Professor Frank Luyten, who is an expert in the field of rheumatology. Additional data are provided in this declaration, demonstrating that the markers identified using the nude model are reliable markers for the ability of cells to produced stable hyaline cartilage *in vivo*, more particularly when injected into a cartilage defect. Indeed, the identification of markers of chondrocyte phenotypic stability using the nude mouse

model has been used for chondrocytes. The expression of these markers by a chondrocyte cell population was indeed found to correlate to the ability of the population to restore a chondrocyte defect. Accordingly, these data further demonstrate that the expression of markers identified by the nude mouse model is a reliable indicator of *in vivo* therapeutic effectiveness of a cell population. It is emphasized that these data demonstrate therapeutic value in humans rather than in an animal model.

Finally, the Examiner asserts "the use of the invention in a therapeutic context would require the precursor cells to differentiate into chondrocytes *in vivo* in order to provide therapy" (Office Action, page 9). Applicants point out that, in Example 7, cell cultures obtained according to the invention were implanted in mice and the resulting implants were then analyzed for their cellular composition. Table 2 of the specification indicates that in 7 out of 8 experiments, chondrocytes were detected in those implants, indicating that the injected precursor cells had indeed differentiated into chondrocytes *in vivo*. Therefore, Applicants have provided clear-cut evidence that the skeletal precursor cells, identified according to the present invention, yielded chondrocytes *in vivo* and could reasonably be expected to function in repairing joint defects.

As for the Examiner's reliance on Hui et al., Applicants' present amendments to the claims and arguments presented above render it moot. Indeed, the specification teaches how to select a particular population of cells from periosteum, bone marrow, or synovial membrane using the positive and negative markers described, and to use those cells in therapeutic compositions adequate for cartilage repair, as shown by the development of chondrocytes *in vivo*.

For all of the aforementioned reasons, applicants' specification fully enables the practice of the claimed invention and it is respectfully requested that the enablement rejection be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph (written description)

Claims 43-45, 61, and 63-64 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In view of the presently amended claims, Applicants submit that the rejection of claims 43-45, 61, and 63-64 is rendered moot and request the withdrawal of said rejection.

Rejections under 35 U.S.C. § 112, second paragraph (indefiniteness)

Claims 43, 45, and 64 were rejected under 35 U.S.C. § 112, second paragraph as failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner argues that the metes and bounds of the term "purified" cannot be ascertained. Applicants respectfully disagree.

Applicants submit that it is well within the knowledge of one of skill in the art to comprehend the implications of the term "purified" with regard to cell culture and composition including such cells. Moreover, applicants note that –"if the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more," *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed.Cir.1985) – the claims clearly are definite. The claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits. However, without acquiescence to this assertion, the currently presented claims are directed to a population of cells positively selected for expressing the CDMP-1 marker, to the exclusion, as technically possible, of cells not sharing this characteristic.

Rejections under 35 U.S.C. § 102(b)

Claims 43, 44, 61, and 64 were rejected under 35 U.S.C. § 102(b) as being anticipated by Takahashi et al; claims 43-45, 61, and 63-64 were rejected under 35 U.S.C.

§ 102(b) as being anticipated by Erlacher et al; and claims 43-45, 61, and 63-64 were rejected under 35 U.S.C. § 102(b) as being anticipated by Chang et al. As applied to the amended claims, these rejections should be withdrawn.

Claim 43, as amended, is directed to "[a] purified homogenous culture of viable, differentiated precursor cells isolated from periosteum, bone marrow, or synovial membrane, that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue, wherein the cells express a positive embryonic marker which is CDMP-1 (emphasis added)."

Claim 44, as amended, is directed to "A therapeutic composition comprising a homogenous culture of viable, differentiated precursor cells, isolated from periosteum, bone marrow, or synovial membrane and expanded, that have entered a post-natal skeletal differentiation pathway leading to skeletal or connective tissue, wherein the cells express a positive embryonic marker which is CDMP-1 (emphasis added)."

As presently amended, the claims are directed to a "homogeneous culture of viable, differentiated precursor cells..." The cells obtained by Takahashi are a mixture of cells, some expressing CDMP-1, some not, as evidenced by the first paragraph of the discussion on page 547 ("although not all the multinucleated cells formed in bone marrow cultures have characteristics of osteoclasts..."). Takahashi et al. therefore do not anticipate claims 43, 45, 61, and 64.

Turning to Erlacher et al., applicants note that Erlacher et al. showed the presence of CDMP-1 and CDMP-2 in adult bovine and human articular cartilage through various methods, including cartilage explants, immunohistochemistry, and cell culture. Erlacher et al. did not actively select precursor cells based on that expression. As shown in Figures 2 and 3 of the reference, a discrete staining was performed for CDMP-1 and CDMP-2, meaning that not all cells expressed either one of these markers. The cell populations obtained by Erlacher et al. are therefore heterogeneous. Erlacher et al. therefore do not anticipate claims 43, 45, 61, and 63-64.

Finally, applicants note that Chang et al. teach "partially purified extracts from newborn calf articular cartilage." Such partially purified extracts cannot be considered homogenous as required by the claims. Chang et al. therefore do not anticipate claims 43, 45, 61, and 63-64.

It is noted that both Erlacher et al and Chang et al. relate to expression of CDMP-1 in articular cartilage. It is clear that the main cell type present in articular cartilage is chondrocytes, but may include e.g. immature chondrocytes or precursor cells. Both Erlacher et al. and Chang et al. refer to the expression of CDMP-1 by "chondrocytes"; Erlacher et al. states '*Immunohistochemical staining of cultured bovine articular cartilage specimens revealed the presence of the CDMPs in most of the chondrocytes*' (page 265, Results, second paragraph, first sentence). In the immunohistochemical and in situ hybridization studies, Chang et al. mostly refers to expression in cartilaginous tissue but also states: "CDMP-1 expression was also detected in hypertrophic chondrocytes" (page 28233, left column, third paragraph, lines 11-12). Accordingly, it is clear that the prior art populations expressing CDMP-1 are heterogeneous and contain at least a sub-population of chondrocytes. Accordingly, Erlacher et al and Chang et al. do not disclose a homogenous population of differentiated precursor cells expressing CDMP-1.

While these prior art publication appear to attribute at least part of CDMP-1 expression to chondrocytes, the present invention demonstrates that whenever a skeletal precursor cell undergoes differentiation such as towards the chondrocytic phenotype, entering a specific differentiation pathway is always preceded by the downregulation of the expression of CDMP-1. This is in line with the data provided by Erlacher et al and Chang et al. demonstrating that in articular cartilage extracts or sections comprising mainly chondrocytes, only a limited number of cells are positive for CDMP-1.

The present invention relates to cultures of differentiated precursor cells, i.e., cells that are capable of differentiating into chondrocytes, but have not yet differentiated into chondrocytes, and demonstrates that these precursor cells are characterized by CDMP-1

expression. While limited numbers of these cells may be present in cartilage extracts, the invention indicates that these precursor cells can be easily isolated from easily accessible sources such as periosteum, bone marrow, and synovial membrane, such as to obtain homogenous cultures of these cells.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such is respectfully requested.

Enclosed is a Petition to extend the period for replying to the final Office action for 3 months, to and including June 15, 2007, and a check in payment of the required extension fee. Also enclosed is a Notice of Appeal.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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James D. DeCamp
Reg. No. 43,580

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045